Review Article ISSN 2639-944X

Journal of Medical - Clinical Research & Reviews

Diagnostic Value of Urine Cytology for Detection of Bladder Cancer

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Received: 07 January 2020; **Accepted:** 25 January 2020

Citation: Kurnia Penta Seputra, Agung Adhitya, Taufiq Nur Budaya, et a. Diagnostic Value of Urine Cytology for Detection of Bladder Cancer. J Med - Clin Res & Rev. 2020; 4(1): 1-4.

ABSTRACT

Introduction: *Malignancy as one of unresolved health problems globally is shown to be the second highest cause of death in the world. One of the most common cancer in Indonesia is the urothelial cancer, this type of cancer placed eighth among all cancer with bladder cancer as the second highest urothelial cancer type. At this point, there is no routine effective bladder cancer screening test. Urine cytology examination of a urine specimen is a simple, safe, and inexpensive method but highly dependent on the skill of the examiner. The aim of the present study was to test the value of urinary cytology in the diagnosis of bladder cancer at Dr. Saiful Anwar General Hospital Malang.*

Methods: *216 patients diagnosed with bladder tumor by histopathological urinary cytology test. The positive cytology categories by papanicolaou classification. The efficacy of urine cytology for detection bladder tumor was determined by calculating its sensitivity, specificity, positive predictive value (PPV), Negative predictive value (NPV) and Prevalence of disease.*

Results: *From 216 patients, 113 patients (52,3%) had bladder tumor, with the value of sensitivity 51.31% and specificity 88.15%. The positive predictive value was 81.88%, whereas the negative predictive value was 64.36%, with the prevalence of disease 50.59%.*

Conclusion: *Urine cytology has high specificity with intermediate sensitivity. The highest sensitivity of urine cytology when used to diagnosed muscle invasive with metastatic bladder cancer. Urine cytology should always be confirmed histologically before definitive therapy.*

Keywords

Bladder Tumor, Sensitivity, Specificity, Urine Cytology.

Introduction

Tumor is an abnormal cell growth that is able to invade and spread through metastasis. According to American Cancer Society report (2011), bladder tumor was the 4th most common tumor occurring in males and 12th most common in females. This tumor also was the 13th most causes for death with 150,200 deaths in 2008. Bladder tumor is a malignant tumor arising from transitional epithelial cell that covers the bladder mucosal layer. Bladder tumors with the most prevalence in developing countries is the urothelial tumor type, occurring as much as 90-95%. Whereas other types found are squamous cell tumors (1.5%), adeno-tumors (1.2%), and small cell tumors (< 1%) [1]. Worldwide incidence for bladder tumor is 9 cases per 100,000 for males and 2 cases per 100,000 for females [2]. In Europe, incidence for bladder tumor can reach 27 cases per 100,000 for males and 6 cases per 100,000 for females. The incidence in Indonesia is yet to be identified. The incidence in Indonesia reaches 5.8 cases per 100,000 inhabitants [3].

According to data from Hasan Sadikin Hospital in Bandung in the last 7 years there were 351 cases of bladder tumors with a mean age of 60.8 years, where the highest number of patients were> 60 years old. Furthermore, at Cipto Mangunkusumo Hospital and Dharmais cancer Hospital in Jakarta, there were 340 patients with bladder tumors during the period January 1995 - December 2004, where there was an increase of around 15% per year in both hospitals with an average age of 54 years old [4]. Whereas from the results of this Study during the period January 2012 to December 2016 it was found that the highest number of patients with bladder tumors were 55 to 64 years old.

The most common ways to diagnose bladder cancer include cystoscopy and biopsy, imaging methods, urinary cytology, fluorescence in situ hybridization, and urine protein detection (BTA-STAT, BTA-TRAK, NMP22 and ACCU-DX). All diagnostic methods for clinical use have their own pros and cons; therefore, it becomes a top priority to find a method of detection and diagnosis of bladder cancer that is characterized by high sensitivity, high specificity, low cost, non-invasive nature, ease of use and good reproducibility. The diagnosis for bladder tumor is made by urine cytology and cystoscopy examination. Urine cytology assessment is the standard assessment before doing a cystoscopy examination for patients with suspected bladder tumor. However, cystoscopy is an invasive examination and can cause pain, bleeding, urinary tract infections and other complications. In addition, it is sometimes difficult for cystoscopy to detect cancer in secluded corners of the bladder, which constrains its clinical application. Meanwhile, urinary cytology is a non-invasive test that can directly identify cancer cells shed in the urine. It is simple to use and inexpensive and performs well, although it has low sensitivity and low diagnostic efficiency, especially with low-grade bladder cancer [2].

Gold standard diagnostic examination for bladder tumor is by histopathology examination, but urine cytology is one important modality to detect urothelial neoplasm [4]. Accuracy for urine cytology depends on a few factors, particularly associated with the degree of tumor, specimen properties, and sample handling. It has been long known that urine cytology was very accurate in diagnosing High Grade Urothelial Carcinoma with cytohistologic correlation of 98%. On the contrary, this assessment has lower sensitivity for Low Grade Tumor cases. Results from this assessment also depends on pathologist's experience in assessing [5]. There were no data reported in Saiful Anwar Hospital Malang about urine cytology examination for the diagnosis of bladder tumor. Therefore, this study aims to identify the value of urine cytology in the diagnosis of bladder tumor in Saiful Anwar Hospital Malang.

Materials and Methods

The design for this study was retrospective cross-sectional study. The sample used in this study were 216 patients who diagnosed histopathologically as bladder tumor in Saiful Anwar Hospital, Malang. The independent variable used in this study was bladder tumor and the dependent variable was urine cytology examination. Patients who diagnosed of bladder tumor, patients whom were histopathologically assessed, and patients managed with either operative or non-operative management are the inclusion criteria. Data was recorded from patients' medical record in Saiful Anwar Hospital Malang from January 2012 – December 2016. Basic characteristic of patients consists of sex and age. Age were than divided by < 34 yo, 35-44 yo, 45-54 yo, 55-64 yo, 65-74 yo, > 75 yo. Histopathologic characteristic (No Muscle Invasive, Muscle Invasive, Muscle Invasive and metastatic, Urothelial, Non-Urothelial, Low Grade, High Grade) were recorded. The efficacy of urine cytology for detection bladder tumor was determined by calculating its sensitivity, specificity, positive predictive value (PPV), Negative predictive value (NPV) and Prevalence of disease. Data was managed using Ms Excel. Sensitivity analysis was intended to show the ability of urine cytology examination in detecting the presence of tumor cells, while specificity analysis showed the ability of urine cytology in identifying the absence of tumor cells. The urine cytology examination would be called positive if the result was in class IV and V of the Papanicolaou classification. This study has been approved by Ethical Committee of Medial and Health Research, Faculty of Medicine Brawijaya University (400/055/K.3/302/2019).

Results

Based on the study results, 216 bladder tumor patients were found in Saiful Anwar Hospital Malang in January 2012 – December 2016. According to Table 1, if clustered by gender, the female group consists of 45 patients (21%), and the male group 171 patients (79%). If clustered by age group, patients ≤ 34 years old consists of 13 patients (6%), age 35-44 years old consists of 19 patients (9%), age 45-54 years old consists of 33 patients (15%), age 55-64 years old consists of 63 patients (29%), age 65-74 years old consists of 51 patients (24%), and age ≥75 years old as much as 37 patients (17%).

		Amount	Percentage
Gender	Male	171	79%
	Female	45	21%
Age	≤ 34 yo	13	6 %
	35-44 yo	19	9%
	45-54 yo	33	15%
	55-64 yo	63	29%
	65-74 yo	51	24%
	≥ 75 yo	37	17%

Table 1: Bladder tumors based on epidemiology characteristics.

As seen in Table 2, based on the histopathologic characteristic, non-muscle invasive bladder tumor was found in 69 patients (32%), muscle invasive tumor was found in 110 patients (51%), and muscle invasive tumor with metastasis found in 37 patients (17%). Based on the tumor type, urothelial tumor was found in 175 patients (81%), and non-urothelial tumor was found in 41 patients (19%). Based on the tumor invasiveness, low-grade tumor was found in 139 patients (64%), and high-grade tumor was found in 77 patients (36%).

Histopathology Characteristic	Amount	Percentage
Non Muscle Invansive	69	32 %
Muscle Invansive	110	51 %
Muscle Invansive + Metastatic	37	17 %
Urothelial	175	81 %
Non Urothelial	41	19 %
Low Grade	139	64 %
High Grade	77	36 %

Table 2: Bladder tumors based on histopathological characteristics.

Based on Table 3, 113 bladder tumor patients showed positive results in their urine cytology examination, and the other 103 showed negative results, with the value of sensitivity and specificity 51.31% and 88.15%, respectively. The positive predictive value was 81.88%, whereas the negative predictive value was 64.36%, with the prevalence of disease 50.59%. In 69 patients with non-muscle invasive tumor, 42 showed a positive result in urine cytology examination and 27 others showed a negative result. The value of sensitivity showed 60.87%. The positive predictive value was 62.69%, whereas the negative predictive value was 87.32%, with the prevalence of disease 24.64%. In 110 patients with muscle invasive tumor, 75 showed a positive result in urine cytology examination and 35 others showed a negative result. The value of sensitivity showed 68.18%. The positive predictive value was 75.00%, whereas the negative predictive value was 84.16%, with the prevalence of disease 34.27%. In 37 patients of muscle invasive tumor with metastasis, 27 showed a positive result in urine cytology examination and 10 others showed a negative result. The value of sensitivity showed 72.97%. The positive predictive value was 51.92%, whereas the negative predictive value was 88.15%, with the prevalence of disease 19.77%.

In 175 patients with urothelial tumor, 79 showed a positive result in urine cytology examination and 96 others showed a negative result. The value of sensitivity showed 45.14%. The positive predictive value was 75.96%, whereas the negative predictive value was 65.96%, with the prevalence of disease 45.34%. In 41 patients with non-urothelial tumor, 23 showed a positive result in urine cytology examination and 27 others showed a negative result. The value of sensitivity showed 56.1%. The positive predictive value was 47.92%, whereas the negative predictive value was 91.18%, with the prevalence of disease 16.27%.

In 139 patients with low-grade tumor, 67 showed a positive result in urine cytology examination and 72 others showed a negative result. The value of sensitivity showed 48.2%. The positive predictive value was 72.83%, whereas the negative predictive value was 72.09%, with the prevalence of disease 39.71%. In 77 patients with high-grade tumor, 43 showed a positive result in urine cytology examination and 34 others showed a negative result. The value of sensitivity showed 55.84%. The positive predictive value was 63.24%, whereas the negative predictive value was 84.55%, with the prevalence of disease 26.74%.

		Urine Cytology		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Disease Prevalence
		Positive	Negative					
Bladder Cancer Histopathology Result	Tumor	113	103	52.31%	88.15%	81.88%	64.36%	50. 59 %
	No Tumor	25	186					
Bladder Cancer Histopathology Charasteristic				Sensitivity				
Non Muscle Invansive	Tumor	42	27	60.87%		62.69%	87.32%	24.64%
Muscle Invansive	Tumor	75	35	68.18%		75.00%	84.16%	34.27%
Muscle Invansive + Metastatic	Tumor	27	10	72.97%		51.92%	88.15%	19.77%
Urothelial	Tumor	79	96	45.14%		75.96%	65.96%	45.34%
Non Urethelial Cell	Tumor	23	18	56.10%		47.92%	91.18%	16.27%
High Grade	Tumor	67	72	48.20%		72.83%	72.09%	39.71%
Low Grade	Tumor	43	34	55.84%		63.24%	84.55%	26.74%

Table 3: Differences in tumor characteristics on positive and negative predictive values on urine cytology examination with sensitivity and specificity.

Discussion

Bladder cancer is the 9th most common cancer worldwide and the second most common malignancy in the urogenital system after prostate tumors. Bladder tumor in early stage are superficial tumor over time the tumor infiltrate into the lamina propria, muscles, and perivesical fat which then spread directly to the surrounding tissue. According to studies that have been carried out, these tumors are twice more common in men than women [4]. Worldwide incidence is 9/100,000 for men and 2/100,000 for women. In Europe, the incidence of bladder tumors reached 27/100,000 for men and 6/100,000 for women [2]. From the results of this study the result during the period of January 2012 to December 2016 found that out of 216 people diagnosed with Bladder tumor, 171 of them were male.

Bladder tumors that are often encountered in developing countries are urothelial tumors or transitional cell tumors, as many as 90-95%. While other types commonly referred as non-urothelial tumors (non-transitional cell tumors) like squamous cell tumors (1.5%), adenotumor (1.2%), and small cell tumors (<1%) [1]. Data from Hasan Sadikin Hospital (RSHS) Bandung in the last 7 years there were 351 cases of bladder tumors, 253 cases (72%) were transitional cell tumors [5]. From the research we conducted, it was found that the most common bladder tumor was a urothelial tumor, which was 81%.

Based on research that has been carried out at RSUP Dr. Mohammad Hoesin Palembang Period 2009-2013 there were 71.2% types of high-grade urothelial carcinoma and 28.8% types of low-grade urothelial carcinoma [6]. Whereas from this study, it was found that 64% were low-grade bladder tumors and 36% were high-grade bladder tumors.

Urine cytology is the most specific examination and is equivalent to cystoscopy in the detection and screening of bladder tumors. Urine cytology attempts to diagnose bladder cancer by counting

the cancer cells in a urine sample, shed from the lining of the bladder [7]. Urine cytology could easily differentiate benign from malignant cells showing high specificity for detecting HGUC (High Grade Urothelial Carcinoma). The cytological features of HGUC showed that the smears exhibited high cellularity and dehiscence cellular pattern. Malignant cells were larger than normal cells and showed pleomorphic nuclei with prominent nucleoli. Also, the cytoplasm ranged from homogenous to scant vacuolated one [8]. The cellularity of samples partially depends on the type of specimen, namely larger number of malignant cells is found in bladder washing, while the cell degeneration with pyknosis is more pronounced in voided urine samples. Sensitivity of cytology for the detection of invasive urothelial carcinoma is high (81-100%) [9]. According to research on the diagnostic significance of several types of bladder tumor examinations carried out in RSUD dr. Moewardi in Surakarta, obtained urine cytology sensitivity of 73.9% (moderate) and specificity of 57.1% (low) [10]. Whereas from this research, the significance of the diagnosis of urine cytology examination was 52.31% and 88.15% specificity.

This study has some limitations. The most important are the somewhat limited nature of the Likert scale used to assess patient satisfaction and the absence of data for partner satisfaction. On the other hand, the strengths of the study include (but are not limited to) that it is based on a large multicenter prospective database with long follow-up; that the outcomes and satisfaction with different types of prosthesis are presented; and that complications are carefully categorized and thoroughly analyzed.

There are certain limitations to this study. variety of urinary tumor markers such as UBC, CYFRA 21-1 and NMP22 appeared to be non-invasive alternative methods for the detection of bladder cancer. Furthermore, the study compared individual and combined sensitivity of the urinary tumor markers in the detection of bladder cancer, contrasting them with the conventional diagnostic procedures.

Conclusion

Urine cytology examination showed high specificity and moderate sensitivity. High sensitivity examination of urine is found in muscle invasive tumors with metastasis bladder tumor. Urinary cytology examination must always be confirmed histologically before definitive therapy.

Acknowledgments

This study was supported by Department of Urology Faculty of Medicine Brawijaya University Malang and Saiful Anwar General Hospital Malang.

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